FORM-PTO-1390 (Rev. 10-96) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 003300-506

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): Unassigned 09/155642

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/SE97/00721	29 April 1997	30 April 1996

300 Rec'd PCT/PTO 02 OCT 1998

TITLE OF INVENTION: BIOLOGICALLY ACTIVE COMPOSITION

APPLICANT(S) FOR DO/EO/US: Åke Lindahl and Rickard Bryland

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:

    International Preliminary Examination Report for PCT/SE97/00721

    A certified copy of the priority application, Swedish Application 9601665-4, filed 30 April 1996, was duly filed in connection with PCT/SE97/00721 and was received by DO/EO/US. Thus, it is believed that the priority claim has been properly substantiated.

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Unassigned	PCT/SE97/00721	003300-506

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $930		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $720.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $790.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1070.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $98.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1,070.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0.00	

Claims	Number Filed	Number Extra	Rate		
Total Claims	34 -20 =	14	X$22.00	$ 308.00	
Independent Claims	2 -3 =	0	X$82.00	$ 0.00	
Multiple dependent claim(s) (if applicable)			+$270.00	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1,378.00	
Reduction for 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 0.00	
SUBTOTAL =				$ 1,378.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
TOTAL NATIONAL FEE =				$ 1,378.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$ 1,418.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ 1,418.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 02-4800 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4800. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Benton S. Duffett, Jr.
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SIGNATURE

Benton S. Duffett, Jr.
NAME

22,030
REGISTRATION NUMBER

PATENT
Attorney Docket No. 003300-506

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	**BOX PCT**
Åke Lindahl and Rickard Bryland	)	Attn: DO/EO/US
Serial No.: corresponds to PCT/SE97/00721	)	Group Art Unit: Unassigned
Filed: October 2, 1998	)	Examiner: Unassigned
For: BIOLOGICALLY ACTIVE COMPOSITION	)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The above-identified application corresponds to PCT/SE97/00721.

Please amend the Application as indicated.

In the Abstract of the Disclosure

Please add the Abstract of the Disclosure submitted on a separate sheet herewith.

In the Claims

Please cancel Claims 29-31 without prejudice, amend Claims 4, 6, 7, 11, 12, 15, 18, 20 and 22-27, and add new Claims 33-37 as follows:

Claim 4, lines 1 and 2, delete "any one of the preceding claims" and insert

--Claim 1--.

Claim 6, lines 1 and 2, delete "any one of the preceding claims" and insert

--Claim 1--.

Claim 7, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 11, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 12, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 15, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 18, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 20, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 22, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 23, lines 1 and 2, delete "any one of Claims 12-22", and insert --Claim 12--.

Claim 24, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 25, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 26, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 27, lines 1 and 2, delete "any one of the preceding claims", and insert

--Claim 1--.

Claim 32, line 2, delete "any of Claims 1-29", and insert --Claim 1--.

Please add the following new Claims 33-37:

--33. A method of prophylactic or therapeutic treatment of a dermatological condition comprising topically applying a prophylactically or therapeutically effective amount of an active agent containing solid composition according to Claim 1, wherein the active agent is suitable for treatment or prophylaxis of a dermatological condition.

34. The method of Claim 33, wherein the active agent is selected from the group consisting of a steroid, vitamin, biologically active lipid, fatty acid, antimicrobial, and anesthetic.

35. The method of Claim 33, wherein the active agent is selected from the group consisting of a corticosteroid, sex hormone, vitamin A, vitamin B2, vitamin B3, vitamin E, vitamin K, an antibiotic, an antiviral, anti-protozoal, antifungal, and an amide local anesthetic.

36. The method of Claim 33, wherein the active agent is selected from the group consisting of clobetasol or a salt or ether thereof, and beta-methasone or a salt or ester thereof.

37. The method of Claim 36, wherein the active agent is clobetasol propionate, methasone-17-valerate or betamethasonedipropionate.--

REMARKS

Claims 4, 6, 7, 11, 12, 15, 18, 20, 22-27, and 32 have been amended in order to remove multiple dependencies therefrom.

New Claims 33-37 have been added to more particularly point out and distinctly claim the subject matter which the Applicant regards as his invention. Support for new Claims 33-37 may be found in the original claims et seq.

Favorable consideration on the merits is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, LLP

By: _____

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Date: October 2, 1998

Abstract of the Disclosure

A biologically active stick composition comprising a biologically active agent dissolved in a carrier system including an unsaturated fatty acid alcohol in mutual dissolution with an alkylene glycol as a solvent for said biologically active agent and a stiffening agent therefor, said stiffening agent imparting stick consistency to the composition, said alkylene glycol preferably being present in an amount of more than 12%. The composition can be prepared by dissolving the active agent in the solvent, combining the solution with the stiffening agent and shaping the formulation into a stick. The composition is especially intended for use as a medicament, preferably in the treatment of dermatological conditions, where it has been found to possess outstanding bioavailability properties.

BIOLOGICALLY ACTIVE COMPOSITION

TECHNICAL FIELD

The present invention relates to the field of biologically active compositions and, in particular, to a biologically active stick composition. Preferably the invention relates to pharmaceutical compositions but, other applications outside the medical field are possible within the scope of the invention.

The invention also relates to the use of such compositions as medicaments and for the manufacture of stick medicaments for treating dermal conditions, as well as to a process for the preparation of such compositions.

BACKGROUND OF THE INVENTION

One of the problems associated with topical medical treatment with high potency drugs is in the application of the composition. Most compositions intended for dermatological treatment of the skin are based on cream, ointment of gel vehicles and, when these are applied to the skin, the incidence of extralesional treatment can be substantial; areas surrounding the lesion to be treated as well as the fingers used to apply a product can be affected by the drug.

By using stick compositions having higher viscosities, which can be housed within a protective package, such extralesional treatment can be avoided or at least substantially eliminated. Another advantage of stick formulations is that, by their use, it is simple to achieve a uniform distribution of drug over the lesion to be treated.

Stick based products are not novel in the treatment of skin conditions and several active compounds have been formulated into sticks. Stick compositions, as herein referred to, are formed from erodible, usually soft and waxy materials having a solid consistency. When rubbed across the skin, such compositions are eroded and deposit a coating of their constituent material on the skin. Ge-

nerally, stick compositions include mixtures of lipids and surfactants as carriers.

A major drawback of those stick compositions used today, however, results from the fact that many drugs, at best, are only marginally soluble in their lipid based formulations and, therefore, must be incorporated into stick compositions as suspended solid particles. This, however, leads to several disadvantages, the most serious one being sedimentation of the active ingredient during manufacture. The method used to manufacture stick compositions involves heating, mixing, packing and cooling and, during the heating, mixing and cooling steps, the viscosity of the lipid mixture can be sufficiently low to allow the suspended active drug to settle. The resulting sedimentation of the active ingredient reduces the homogeneity of the composition and can prevent the product from meeting the standards required for pharmaceutical products.

Several solutions to the sedimentation problem have been proposed. Some are based on mechanical measures, which involve regularly turning any vessel used to accomodate the composition before it has set, so that the drug particles are maintained in a suspended state. Others involve the addition of thickening agents to form thixotropic gels. None of these proposals, however, have enabled the manufacture of homogeneous formulations in a reproducible way.

Another disadvantage with topical formulations in general, and stick formulations in particular, is the poor bioavailability of the active drug to the skin. For topical dermatological formulations containing corticosteroides, bioavailability can be in the order of a few percent. Low bioavailability has many implications. One is that the effect of a drug can be variable and non-reproducible, both at the site of application and systemically. Another is that, when conditions at the site of

application are favourable for the penetration of a drug, systemic concentrations thereof can reach toxic levels.

A corticosteroid stick product containing propylene glycol or 1,3-butylene glycol is previously known from US 4,299,828. However, said product is not based on the use of an unsaturated fatty acid alcohol as a solvent and the alkylene glycols referred to are not utilized as solvents but rather as anti-microbial compounds. Furthermore, it is specifically stated that said anti-microbial compound is not dissolved in the stick but dispersed therein (col 3 lines 35-40 and claim 1), i.e. the stick is not a homogeneous product. In addition thereto the preferred percentage of the alkylene glycol is disclosed as 2-10 and optionally 3-8 % by weight (col 3 lines 20-22 and claim 1). Thus, the purpose of the alkylene glycol is completely different from that of the present invention where higher percentages of alkylene glycol have been found to give other effects than those referred to in US 4,299,828.

DESCRIPTION OF THE INVENTION

The present invention relates to a completely novel solid composition, especially a stick composition, for biologically active agents, which may seem similar to the aforementioned lipid based stick products, but which is of a completely different structure and thereby possessed of completely different properties as compared thereto.

More specifically, the solid compositions according to the present invention do not rely upon mechanical means to ensure uniform distribution of the biologically active agent. The active agent is distributed in a lipid carrier, but not in a suspended or dispersed state as previously practised but, rather, in a dissolved state. Thus, it has unexpectedly been found that, in spite of the generally poor solubility of the biologically active compounds previously formulated in stick compositions, a more or less complete dissolution of the biologically ac-

tive agent can be obtained by means of the present invention into a completely homogeneous solid composition.

A first object of the invention is to provide a composition which contains a biologically active agent in a dissolved state.

Another object of the invention is to provide a composition which possesses an enhanced stability against sedimentation of the active agent.

Still another object of the invention is to provide homogeneous compositions.

One other object of the invention is to provide compositions possessing an enhanced release rate for the active agent, i.e. improved bioavailability, especially for use in dermatology.

Still another object of the invention is to provide compositions, the consistency of which can be controlled by means of the composition thereof, especially to accomplish a composition to be administered via the skin.

One other object of the invention is to provide a composition for use as a drug or medicament, especially for the treatment of dermatological conditions.

Still another object of the invention is to provide a process for the preparation of compositions, especially stick compositions of the type referred to above.

Still other objects of the invention should be obvious to a person skilled in the art after having studied the following description of the invention.

Thus, according to a first aspect of the present invention there is provided a solid composition comprising a biologically active agent dissolved in a carrier system, wherein the carrier system includes a specific combination of solvents for the active agent and a stiffening agent for imparting a solid consistency to the composition. Preferably, the stiffening agent is a viscosity enhancing agent capable of imparting a soft and erodible consistency to the composition.

It is preferred that compositions in accordance with

the present invention are stick compositions as hereinbefore defined.

More specifically a solid composition is claimed, wherein the carrier system includes an unsaturated fatty acid alcohol in combination with an alkylene glycol selected from propylene glycol, butylene glycol, dipropylene glycol and/or dibutylene glycol as a solvent for the active agent and a stiffening agent for imparting a solid consistency to the composition, said alkylene glycol being present in an amount that gives mutual dissolution with said unsaturated fatty acid alcohol as well as dissolution of said active agent.

By employing the present invention, it is possible to combine the good characteristics of a homogeneous solution with the good characteristics of a stick products, which combination has hitherto not been possible.

As the carrier system preferably comprises miscible solvent and viscosity enhancing substances, compositions in accordance with the invention can form stable stick compositions without any substantial sedimentation of the biologically active agent.

Furthermore, the solvent combination used should be capable of dissolving the biologically active agent at a temperature where significant decomposition of said agent is avoided.

Generally, the biologically active agent is any biologically active compound, or mixture of compounds, which can be dissolved to a substantial extent in the carrier system of the present invention. Typically, this means that the biologically active agent is a lipophilic, i.e. lipid soluble, compound. In this context the invention is of special interest in connection with drugs or medical compounds but, of course, the inventive idea is applicable to any biologically active agent for which a stick formulation is appropriate. The term "biologically active agent" should be interpreted in a broad, conventional

sense to mean an element, compound or composition which, when present in an effective amount, will interact with living organisms, preferably to elicit a therapeutic effect.

There are a large number of agents falling within the avove-mentioned definitions and which can be formulated in compositions according to the invention. However, some specific examples include steroids, e.g. corticosteroids, vitamins, sex hormones, biologically active lipids, fatty acids, antibiotics or antimicrobials and local anestetics. In this connection it should be noted that, as is common in the art, the compounds can be used per se or in the form of salts or esters or other chemically modified forms thereof.

Some examples within the above-mentioned groups include vitamins A, D2, D3, E, K and derivatives thereof, androgens, estrogens and derivatives thereof, amide type local anestetics and antimicrobials such as antivirals, antibacterials, antiprotozoals and antifungals. Further examples include fluocinonide, omega-3-fatty acid and azelaic acid, and salts and esters thereof, clobetasol, and salts and esters thereof, and betamethasone and salts and esters thereof, particularly betamethasone-17-valerate and betamethasonedipropionate.

Generally the solvent used is capable of dissolving the specific active agent used to the desired extent. Preferably the solvent comprises an unsaturated C_{16}-C_{20}-fatty acid alchol, more preferably C_{18}-fatty acid alcohol, in mutual dissolution with the alkylene alcohol referred to. In the case of said unsaturated C_{18}-fatty acid alcohol, it is preferably selected from oleyl alcohol, ricinolyl alcohol, linolyl alcohol and/or linolenyl alcohol and more preferably is oleyl alcohol. Another example of a C_{18}-fatty acid alcohol is eleosteryl alcohol, while a preferable example of a C_{16}-fatty acid alcohol is palmitoleyl alcohol, and a preferable example of a C_{20}-fatty acid alcohol is arachidonyl alcohol.

In more general terms the unsaturated fatty acid alcohol is used in combination with an alkylene glycol having the general formula $R(OH)_2$; a di- or poly-alkylene glycol having the general formula $HOR(OR)_nOROH$; a C_4-C_{36} (e.g. C_4-C_{18}) aliphatic primary alcohol; or a mixture of two or more such compounds. In the foregoing formulae, each group R can be the same or different and is an alkyl, preferably a C_2-C_6 alkyl group and $n \geq 0$. Preferred groups R are ethyl, propyl and butyl groups and the preferred glycols thus include propylene glycol, butylene glycol, dipropylene glycol and dibutylene glycol.

In addition to the above-mentioned unsaturated fatty acid alcohols other primary alcohols can be included in the composition, such as lauryl alcohol, myristyl alcohol, palmityl alcohol and/or stearyl alcohol.

In one preferable embodiment of the invention an additional solvent can be included wich is selected from lipid esters, such as fatty acid esters and esters of sorbic acid. Examples of fatty acids from which such esters can be derived include lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, ricinoleic acid, linolic acid and linolenic acid. The precursor alcohols are preferably the C_1-C_6-alkanols methanol, etanol, propanol, butanol, pentanol and hexanol with either straight or branched carbon chains. Especially preferred esters in this respect are the propyl esters, including the isopropyl esters, especially isopropylpalmitate.

Still further additional solvents usable in the invention are the C_2-C_6 alkylene carbonates, e.g. ethylene, propylene or butylene carbonate, preferably propylene carbonate.

The viscosity enhancing agent should be chosen such that it is compatible with the solvent and so that it imparts the desired viscosity or consistency thereto. Generally this means that said viscosity enhancing agent is a waxy substance.

In preferred embodiments of the invention said waxy substance is a natural or synthetic wax which is generally defined as monoester of a long-chained (typically C_{14}-C_{36}, e.g. C_{18}-C_{24}) carboxylic acid with a long-chained (typically C_{16}-C_{36}) alcohol. In both cases the carbon chains, preferably, are unbranched aliphatic chains.

In another embodiment the waxy substance is a fat and, preferably, a triglyceride of a C_{18}-C_{36} fatty acid or a glycol (typically an alkylene glycol as herein before defined and comprising 2-6 carbon atoms) ester of a C_{18}-C_{36} fatty acid.

Combinations of said waxes and/or waxy substances may be employed and, in an especially preferred embodiment of the invention, the viscosity enhancing agent comprises a combination of a natural and/or synthetic wax plus a triglyceride and/or a glycol ester, as defined above, and enables the carrier system's rheological properties to be accurately tailored, for example, to achieve a broad softening point.

Other preferred waxes are paraffin wax and cerasine wax.

In some cases, the viscosity enhancing agent, or waxy substance, can cause the composition to be too viscous. In accordance with the present invention this can be avoided by incorporating into the carrier system an oil having the capacity to plasticize the viscosity enhancing agent and reduce the viscosity of the carrier system to a level that is suitable for the composition's intended purpose. Preferred plasticizing oils include low molecular weight aliphatic acids and alcohols, especially with branched chains, e.g. fluid lanoline.

When the inventive composition is for use as a medicament, it should hardly need mentioning that all of the above-identified ingredients, as well as other optional conventional further ingredients, should be pharmaceutically acceptable and non-toxic when the composition is used in the intended manner.

The combination of solvent and viscosity enhancing agent in the carrier system should be selected in line with the principles given above such that a proper dissolution rate, consistency and release rate are obtained. Generally this means that the amounts of the different ingredients could be decided experimentally using techniques well known to persons skilled in the art. However, in general the amount of solvent can be within the range of 20-85 % by weight, the amount of viscosity enhancing agent can be within the range of 15-80 % by weight and the amount of plasticizing oil can be within the range of 0- 30 % by weight, based on the total weight of the carrier system.

Preferably the amount of solvent is within the range of 25-75, more preferably 40-60, percent by weight, while the amount of viscosity enhancing agent is within the range of 15-55, more preferably 25-50, percent by weight and the amount of plasticizing oil is within the range of 0-30, more preferably 2-20, percent by weight.

As was mentioned above it has been found possible to combine the unsaturated fatty acid alcohol with the alkylene glycol in such properties that mutual dissolution of the solvents as well as full dissolution of the active agent in the composition is accomplished. Generally this means that the amount of alkylene glycol is more than 12 % by weight and preferably at least 15 % by weight, based on the total weight of the carrier system.

According to an especially preferable embodiment of the invention the amount of the alkylene glycol solvent, preferably propylene glycol, is within the range of 12-23, preferably 15-23, % by weight, based on the total weight of the carrier system, more preferably 12-20, especially 15-20, % by weight.

In another preferable embodiment of the invention, where said additional solvent is present, the weight ratio of oleyl alcohol : additional solvent is within the

range of 1:2 to 5:1, preferably 1:2 to 3:1 and more preferably 1:2 to 2:1.

The amount of the biologically active agent is of course dependent on the effect to be accomplished. Generally, however, the upper limit will be the active agent's solubility limit in the carrier system, which can be up to 40 percent by weight or in some cases merely up to 10 or even 5 percent by weight, in all cases calculated on the weight of the carrier system. Preferably the range thereof can be 0.01 - 10, especially 0.02 - 5, percent by weight, on the same basis. The exact amount, however, is easily determined by a person skilled in the art with reference to the optimum or maximum effect it is wished to obtain.

It is especially preferred that compositions according to the invention are for pharmaceutical or medical purposes. In this case, the biologically active agent can be a therapeutic or prophylactic agent of any kind. The other ingredients employed must be selected in accordance with the general principles applying to the formulation of medical or pharmaceutical compositions.

In an especially preferred embodiment, the inventive composition comprises a medicament for administration to the skin, or for dermal administration. In such a case a person skilled in the art will formulate the composition such that its viscosity will be proper for administration in that way and such that the release of the active compound will have the desired profile.

Thus, from the above-mentioned it should be clear that stick compositions according to the present invention are especially well suited for the treatment of dermatological conditions.

According to yet another aspect of the invention there is also provided a process for the preparation of compositions, preferably stick compositions, in accordance with the invention. Said process comprises dissolving the biologically active agent in the solvent there-

for, combining the resulting solution with a viscosity enhancing agent so as to impart a solid consistency to said solution and shaping the resulting formulation into a stick.

Preferably the active agent is dissolved in the solvent, or part thereof, and the solution obtained is then added to a melted mass of the viscosity enhancing agent, preferably while being stirred. When a homogeneous mass has been obtained, said mass, preferably after some cooling, can then be poured into a mould and allowed to cool and set in the desired shape. Proper temperatures in this respect are easily determined by a person skilled in the art.

The composition is physically stable below +50°C although softening of the structure may occur. The composition should be capable of returning to its original viscosity after cooling to +30°C or lower. This may also be valid after heating to temperatures in excess of +50°C.

After such heating followed by cooling to +30°C or lower the composition will still be homogeneous. This is an advantage compared to such stick formulations where the active drug is in solid form, i.e. suspended. In these compositions the active drug will settle out at higher temperatures and form an unhomogeneous preparation.

EXAMPLES

The invention will now be exemplified further by means of the following non-limiting working examples.

EXAMPLE 1

Stick compositions 1-10 were prepared from the following ingredients, the figures being percentages by weight.

	1	2	3	4	5	6	7	8	9	10
Fluid lanoline	14.3	14.3	12.9	12.9	15.4	16.7	17.6	17.6	18.5	11.9
Paraffin wax	7.1	7.1	6.4	6.4	5.4	3.5	3.7	3.7	-	5.8
Ceresine wax	5.4	5.4	4.9	4.9	5.8	4.7	4.9	4.9	3.9	4.5
Syncrowax ERLC	14.3	14.3	12.9	12.9	8.6	7	-	-	-	11.9
Syncrowax HGLC	10.7	10.7	9.6	9.6	12.9	11.7	14.7	14.7	15.5	8.9
Oleyl alcohol	35.6	35.6	32	32	38.4	41.7	43.7	43.7	46	29.7
Isopropylpalmitate	12.5	12.5	11.2	11.2	13.5	14.6	15.4	15.4	16.1	10.4
Propylene glycol	-	-	10	10	-	-	-	-	-	16.7
Clobetasol propionate	0.05	-	-	-	-	-	-	-	-	-
Betamethasone-valerate	-	0.12	-	-	-	-	-	-	-	-
Fluocinonide	-	-	0.05	-	-	-	-	-	-	-
Betamethasone-dipropionate	-	-	-	-	0.067	0.067	0.067	-	0.067	0.067

The manufacturing process was as follows:

The active agent was dissolved in the oleyl alcohol. Separately the lanoline, paraffin wax, ceresine wax, glycol esters, triglycerides and the isopropyl palmitate were mixed together in a glass beaker.

The mixture in the glass beaker was then heated to about 75°C and was allowed to melt while being stirred. The oleyl alcohol and active agent solution, also heated to +75°C, was then added thereto and the combination was stirred for 10 minutes.

After reducing the temperature to about 65°C the resulting composition was poured into a stick mould and allowed to cool and solidify.

These compositions were then tested by means of conventional blanching tests (blanching is an established method of assaying biological activities of steroid preparations) and compared with commercial creams and ointments. The results of said tests are summarized as follows:

Product	Test mean value
Comp. 1	1.78
2	1.25
3	1.81
4	-
5	1.69
6	1.67
7	1.33
8	0.03
9	1.47
10	2.53
Lidex Ointment x)	2.42
Temovate Ointment xx)	2.75
Betamethasone valerate Ointment (Fougera) xxx)	1.94
Diprolene Cream	2.64
Diprolene Ointment	2.72

x) 0,05% fluocinonide
xx) 0,05% clobetasol propionate
xxx) 0,12% betamethasone valerate

From said results it can be seen that composition No. 10 according to the invention was bioequivalent to all commercial cream and ointment products, which is indeed unexpected and means a great contribution to the art now that a stick product can compete with well-estab-

lished creams and ointments. Furthermore, it should be borne in mind that the new stick claimed possesses great advantages also compared to known stick products as has been described above (completely homogeneous product with no sedimentation problems, etc.).

CLAIMS

1. A solid composition comprising a biologically active agent dissolved in a carrier system, wherein the carrier system includes an unsaturated fatty acid alcohol in combination with an alkylene glycol selected from propylene glycol, butylene glycol, dipropylene glycol and/or dibutylene glycol as a solvent for the active agent and a stiffening agent for imparting a solid consistency to the composition, said alkylene glycol being present in an amount that gives mutual dissolution with said unsaturated fatty acid alcohol as well as dissolution of said active agent.

2. A compostion as claimed in claim 1, wherein the amount of said alkylene glycol is more than 12 % by weight, based on the total weight of the carrier system.

3. A compostion as claimed in claim 2, wherein the amount of said alkylene glycol is at least 15 % by weight.

4. A composition as claimed in any one of the preceding claims, wherein said unsaturated fatty acid alcohol is an unsaturated C_{16}-C_{20}-fatty acid alchol, preferably an unsaturated C_{18}-fatty acid alchol.

5. A composition as claimed in claim 4, wherein said unsaturated C_{18}-fatty acid alcohol is selected from oleyl alcohol, ricinolyl alcohol, linolyl alcohol and/or linolenyl alcohol, preferably oleyl alcohol.

6. A composition as claimed in any one of the preceding claims, wherein the stiffening agent is a viscosity enhancing agent capable of imparting a soft and erodible consistency to the composition.

7. A composition as claimed in any one of the preceding claims, wherein the biologically active agent is a lipophilic compound, preferably a lipophilic drug.

8. A composition as claimed in claim 7, wherein the biologically active compound is selected from steroids, including corticosteroids, sex hormones, including andro-

gens and estrogens and derivatives thereof, vitamins, including vitamins A, D2, D3, E, K and derivatives thereof, biologically active lipids, fatty acids, antibiotics and antimicrobials, including antivirals, antibacterials, antiprotozoals and antifungals, and local anestetics, preferably of the amide type.

9. A composition as claimed in claim 8, wherein the biologically active compound is selected from fluocinonide, omega-3-fatty acid and azelaic acid and salts and eters thereof.

10. A composition as claimed in claim 8, wherein the biologically active compound is clobetasol or a salt or an ether thereof, preferably clobetasol propionate.

11. A composition as claimed in any one of the preceding claims, wherein the alkylene glycol is propylene glycol.

12. A composition as claimed in any one of the preceding claims, wherein the solvent additionally comprises a C_1-C_6-alkanol ester of a fatty acid and/or a C_1-C_6-alkanol ester of sorbic acid.

13. A composition as claimed in claim 12, wherein said additional solvent comprises propyl (incl. isopropyl) myristate, palmitate, oleate, stearate and/or laurate, and/or the propyl (incl. isopropyl) ester of sorbic acid.

14. A composition as claimed in claim 13, wherein said additional solvent is isopropylpalmitate.

15. A composition as claimed in any one of the preceding claims, wherein the viscosity enhancing agent is a waxy substance.

16. A composition as claimed in claim 15, wherein the waxy substance comprises a natural and/or synthetic wax, preferably a monoester of a long-chained carboxylic acid with a long-chained alcohol; a fat, preferably a triglyceride of a C_{18}-C_{36} fatty acid; a glycol ester of a C_{18}-C_{36} fatty acid; or a mixture of two or more such compounds.

17. A composition as claimed in claim 16, wherein the waxy substance comprises a combination of a natural or synthetic wax and a triglyceride and/or a glycol ester.

18. A composition as claimed in any one of the preceding claims, wherein the carrier system also comprises an oil capable of plasticizing the viscosity enhancing agent and reducing the viscosity of the carrier system.

19. A composition as claimed in claim 18, wherein the plasticizing oil is selected from low molecular weight aliphatic acids and alcohols, preferably having branched chains, and preferably is fluid lanoline.

20. A composition as claimed in any one of the preceding claims, wherein the amount of solvent is within the range of 20-85 % by weight, the amount of viscosity enhancing agent is within the range of 15-80 % by weight and the amount of plasticizing oil is within the range of 0-30 % by weight, based on the total weight of the carrier system.

21. A composition as claimed in claim 20, wherein the amount of solvent is within the range of 25-75, preferably 40-60, % by weight, the amount of viscosity enhancing agent is within the range of 15-55, preferably 25-50, % by weight and the amount of plasticizing oil is within the range of 0-30, preferably 2-20, % by weight.

22. A composition as claimed in any one of the preceding claims, wherein the amount of said alkylene glycol is within the range of 12-23, preferably 15-23, % by weight, more preferably 12-20, especially 15-20, % by weight.

23. A composition as claimed in any one of claims 12-22, wherein the weight ratio of unsaturated fatty acid alcohol : additional solvent is within the range of 1:2 to 5:1, preferably 1:2 to 3:1, especially 1:2 to 2:1.

24. A composition as claimed in any one of the preceding claims, wherein the biologically active agent is

present in a concentration of up to the solubility limit thereof in the carrier system.

25. A composition as claimed in any one of the preceding claims, wherein the concentration of the biologically active agent is 0,01-10, preferably 0,02-5, % by weight, based on the weight of the carrier system.

26. A composition as claimed in any of the preceding claims, wherein said composition is a stick composition.

27. A composition as claimed in any one of the preceding claims for use as a medicament, said biologically active agent being a therapeutically or prophylactically active agent.

28. A composition as claimed in claim 27, for topical application to the skin of a mammal, especially man, wherein the composition has a viscosity that is adapted for such application.

29. A composition as claimed in any of the preceding claims, wherein the biologically active compound is betamethasone, or a salt or ester thereof, preferably betamethasone-17-valerate or betamethasonedipropionate.

30. Use of a composition as claimed in any of the preceding claims for the preparation of a medicament for therapeutic or prophylactic treatment of a dermatological condition.

31. A use as claimed in claim 30, wherein the composition is as claimed in any one of claims 2-29.

32. A process for the preparation of a biologically active composition as claimed in any of claims 1-29, comprising dissolving the biologically active agent in said solvent therefor, combining the resulting solution with a viscosity enhancing agent so as to impart a solid consistency to said solution and shaping the resulting composition into a desired form.

COMBINED DECLARATION AND POWER OF ATTORNEY FOR UTILITY PATENT APPLICATION	Attorney's Docket No. 003300-506

As a below-named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR (if only one name is listed below) OR AN ORIGINAL, FIRST AND JOINT INVENTOR (if more than one name is listed below) OF THE SUBJECT MATTER WHICH IS CLAIMED AND FOR WHICH A PATENT IS SOUGHT ON THE INVENTION ENTITLED:

BIOLOGICALLY ACTIVE COMPOSITION

the specification of which

(check one) ☐ is attached hereto;
☒ was filed on 29 April, 1997 as
Application No. PCT/SE97/00721
and was amended on _____;
(if applicable)

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE;

I ACKNOWLEDGE THE DUTY TO DISCLOSE TO THE OFFICE ALL INFORMATION KNOWN TO ME TO BE MATERIAL TO PATENTABILITY AS DEFINED IN TITLE 37, CODE OF FEDERAL REGULATIONS, Sec. 1.56 (as amended effective March 16, 1992);

I do not know and do not believe the said invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application; that said invention was not in public use or on sale in the United States of America more than one year prior to said application; that said invention has not been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than twelve months prior to said application;

I hereby claim foreign priority benefits under Title 35, United States Code Sec. 119 and/or Sec. 365 of any foreign application(s) for patent or inventor's certificate as indicated below and have also identified below any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application(s) on which priority is claimed:

COMBINED DECLARATION AND POWER OF ATTORNEY

Attorney's Docket No. 003300-506

COUNTRY/INTERNATIONAL	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
Sweden	9601665-4	30.04.1996	YES X NO_
			YES_ NO_
			YES_ NO_
			YES_ NO_
			YES_ NO_
			YES_ NO_
			YES_ NO_
			YES_ NO_

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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